

Entropic Studies of Cytoskeletal Motors Jamming

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Abstract

Can the different causes for disruption of intracellular transport be traced from the trajectories of the molecular motors on the cytoskeletal filaments? We will attempt to answer this important question in a Monte Carlo model of microtubule-motor protein interaction from the point of view of information theory.

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Molecular motors (MM) are key means of intracellular transport and therefore control the spatial organization of eukaryotic cells [1]. One intriguing example is provided by the intracellular traffic of MM along cytoskeletal filaments. Microtubule-MM interaction play a crucial role in cellular processes, such as chromosomal segregation during cell division, flagellar motion and axonal transport. Disruption of transport events has been determined to be the molecular basis for many diseases like Alzheimer's disease and motor neuron disease (MND) [2]. Large axonal swellings, spheroids, in the spinal cords of patients with motor neuron disease show massive accumulation of kinesin, major molecular motors responsible for fast axonal transport [3].

Disturbances of cytoskeletal filament transport has been also studied recently from a theoretical point of view [4], finding that hard-core motor-motor interactions produce overcrowding of the motors on the filament near its + end, even at relatively small motor concentration, and this traffic jam then extends towards the – end with increasing concentration of motors. This motor jamming produce also a decrease of the current of motors through the filament.

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The average motor current obtained as a function of the motor concentration is shown in Fig. 1. It can be seen from that figure that a low average motor current may be caused by low motor concentration or by high motor concentration with jamming. Even in this simple model, the average motor current is useless to distinguish the two possible causes of current decrease. Can the different causes of current decrease like overcrowding, low motor density, or other motility problems like those of MND, be traced from the molecular motors trajectories? The entropy of the motor walk seems one possibility that we will study here.

Molecular motors interacting with cytoskeletal filament constitute far from equilibrium, non-ergodic systems and the usual entropy definition depending on probabilistic ensemble concepts are not well suited to describing the information content of this dynamics. Kolmogorov's concept of algorithmic complexity [5] is commonly used in the study of far from equilibrium systems, such as proteins and fractal growth processes, because it was developed to deal with single objects. The algorithmic complexity of an object is broadly defined as the length in bits of the shortest description for that object [5]. The algorithmic complexity of a string of characters is the length in bits of the smallest program that produces as output the string. The problem with this definition is that it is impossible, even in principle, to find such a program. Nevertheless, the zipping file compression programs are based on algorithms that are expected to carry out this task, at least approximately. The Lempel and Ziv algorithm (*LZ77*) [6], used by *gzip* and *zip* is probably the best known file compression algorithm. In this algorithm, the data sequence is parsed into words such that the next word is the shortest word not seen in the past. The coding of this new word is done by a pair of numbers formed by the pointer to the last occurrence of the prefix and the last bit of the new word. Therefore the zipper will encode more frequent sequences with fewer bytes and will use more bytes for rare sequences. It has been shown that [6] when the length of text to be zipped tends to infinity the ratio between the length of the zipped file and the length of the original file tends to h , the entropy per charac-

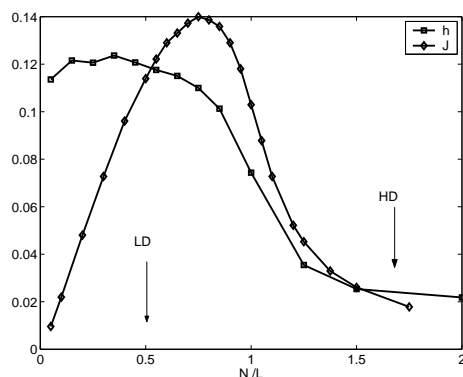


Fig. 1. Plots of the entropy per character h , and average current J , as a function of the linear density N/L of motors.

ter of the ergodic source of the text. The *LZ77* zipper was used recently for language and author recognition[7], to quantify the information transfer in thermal ratchets[8], and in Parrondo's games[9].

We will address the motor dynamics from this point of view of information theory. As the motors either move forward or remain at a fixed site at a given time step, the trajectory of any given motor while bound to the filament is isomorphic to a message composed from an alphabet consisting of two letters. Thus our procedure to analyze the bound motor dynamics is as follows: For a given concentration of motors, every motor trajectory on the microtubule is transformed on a binary message. All these messages are joined into a single string, and the entropy per character of this string is obtained with the zipping method as the ratio between the length of the zipped file and the length of the original file. The entropy per character h obtained in this way is independent of the length of the string and corresponds to the properties of the ergodic source of the string of messages. Specifically h will be the average number of bits of information that we gain on being told that a given motor moves forward or remains immobile at a given site. This procedure is carried out for different concentrations of motors. We use a lattice model developed by Lipowsky, Klumpp and Niewenhuizen [4] to represent the molecular motor traffic along a microtubule. Here we focus on a closed cylindrical compartment as in Fig. 1 of [4] with one microtubule in the center. The motor particle moves on a cubic lattice with lattice constant l . The cylindrical compartment has length $L = 200l$ and radius $L_{\perp} = 25l$. Its + end is at $x = L$. In order to perform MC simulations simulation parameters were chosen in such a way that the lattice random walks have the same bound state velocity, bound and unbound diffusion coefficient D_b and D_{ub} , respectively, and walking time Δt_b as the real motors. The motor particle moves on a cubic lattice with lattice constant l . The microtubule is taken to consist of a one-dimensional line of binding sites. Away from the filament, the hopping rates between any two nearest neighbor sites are equal to $1/6\tau$ where the time scale τ for the unbound motor is given by $\tau = l^2/6D_{ub}$. The motor can adsorb onto a filament binding site with sticking probability π_{ad} . Once the motor is bound, the time scale changes to τ_b . α/τ_b is the forward step rate and ϵ/τ_b the unbinding rate. We ignore backward steps because we are simulating processive motors. Nevertheless, bound state diffusion still occurs because of the nonzero dwell probability defined by $\gamma = 1 - \alpha - 2/3\epsilon$. The dwell probability γ defines the mean dwell time $\tau_{dw} = \tau_b\gamma/(1 - \gamma)$ and the mean step time $\tau_s \equiv \tau_{dw} + \tau_b$. In our MC simulations we focus on two headed kinesin [4] which is experimentally characterized by a filament repeat length $l = 8nm$, a bound state velocity $v_b = 680nm/s$ and a bound state diffusion coefficient $D_b = 1360nm^2/s^2$, which are recovered [4] for $\alpha = 0.4975$, $\gamma = 0.4987$, and $\epsilon = 0.0075$; $\tau_b = 5.9ms$, $\tau_s = 11.8ms$. The bulk diffusion coefficient for unbound motors is taken as $D_{ub} = 4\mu m^2/s$ which implies $\tau = \tau_b/1341$, and $\pi_{ad} = 1$. Within the compartment, the active transport of the motors along the filament produces both, a bound current

J_b , and, a concentration gradient between the two ends of the tube. While the unbound motors give rise to a diffusive current J_{ub} that balances the bound current along the filament resulting in a nonequilibrium steady state distribution of both bound and unbound motors in the axonal compartment. The motion of every motor on the microtubule resulting from the MC simulation is coded into a binary string where **0** and **1** correspond to no motion or a step to the + end of the microtubule respectively as described above. The unbound motor motion is not taken into account. The binary strings obtained for different concentrations of motors were zipped to obtain approximations to the entropy per character h for different motor concentrations. The overall transport along the filament can be characterized by the average current $J = \int dx J_b(x)/L$. The average current J and the entropy per character h as functions of the linear density of motors N/L are shown in Fig. 1. The average current J dependence on the linear density of motors N/L is analogous to the fundamental diagram of traffic models [10] in which the car flow as a function of vehicle density increases linearly for low densities, reaches maximum throughput, and then decays for higher densities. The analogy between both, Nagel's traffic model and our molecular motor model, shows clearly that the scenario is the same for both models, and we may imply that the critical phase transition at maximum throughput of Nagel's traffic model [10] is also present in our model for maximum MM average current. Critical phase transition is associated to divergence of correlation between motors and continuous entropy variation [11] across the transition density point as can be seen in Fig. 1.

A low average motor current may be caused by low motor concentration or by high motor concentration with jamming. Nevertheless the entropy per character h is much higher for the low density (LD) free motion than the corresponding to the high density (HD) jammed regime. This behavior is due to the fact that for low N , motors move nearly free on the microtubule and dwell and step forward probabilities, γ and α , are almost the same. On the other hand, for large N , h decreases because overcrowding limits the stepping forward of the motors. In this way, the **1** that indicates a step towards the + end becomes unusual and the strings are composed mainly by the "motionless" **0**. According to Shannon information theory, entropy measures *how much information is gained when an outcome is observed*. Nothing new is learned when a usual **0** is found, but **1** at the string is a piece of information that decreases the level of uncertainty.

Another important quantity that may be used is the notion of relative entropy or Kullback-Leibler divergence [12] which is a measure of statistical remoteness between two distributions. Recently Ziv and Merhav [13] proposed an algorithm based on a procedure similar to the one used in the LZ77. A nice review of Ziv and Merhav algorithm with interesting applications was done in [14]. We follow the recipe described in [14]: The relative entropy between two distributions of MM trajectories corresponding to different concentrations of

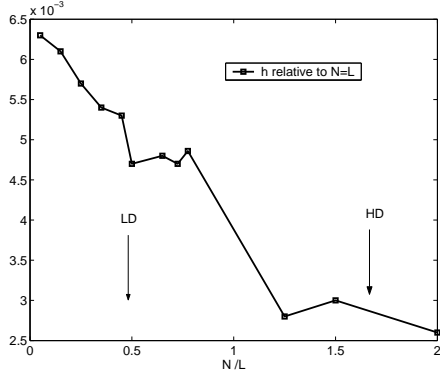


Fig. 2. Estimate of relative entropy between different concentrations and $N = L$, approximate limit between high and low motor density.

motors \mathbf{N}_1 and \mathbf{N}_2 that produce binary strings N_1 and N_2 , respectively, is obtained in the following way: Long sequences n_1 and n_2 are extracted from the binary strings N_1 and N_2 , respectively, and a short sequence n_{2sh} from N_2 . New sequences $n_1 + n_{2sh}$ and $n_2 + n_{2sh}$ are created by appending n_{2sh} to n_1 and n_2 , respectively. The relative entropy per character $h_{N_1 N_2}$ is estimated by

$$h_{N_1 N_2} = \frac{Z_{n_1+n_{2sh}} - Z_{n_1} - (Z_{n_2+n_{2sh}} - Z_{n_2})}{|n_{2sh}|},$$

where Z is the length of the zipped sequence, and $|n_{2sh}|$ is the number of characters of the sequence n_{2sh} . It may be appreciated in Fig. 2 that relative entropy estimates distinguish clearly between the strings that result from high and low motor density dynamics.

In summary, by mapping the molecular motor motion to strings of characters, with data compression techniques we obtained the change of entropy corresponding to the high-low density transition. The overcrowding cause can be distinguished from the low motor density cause of cytoskeletal motor current decrease with the entropy per character h and also by the relative entropy per character $h_{N_1 N_2}$. We will present elsewhere the results for the motor neuron disease simulation.

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